~~98.~~ **(Twice amended)** A method for [modulating] stimulating responsiveness in an anergic T cell, comprising contacting said T cell with an [agent] anti-γ chain antibody which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is [modulated] stimulated.

REMARKS

Claims 48-101 were pending in the application. Claims 49, 51-54, 62-96 and 99-101 have been canceled without prejudice and claims 48, 50, 55, 56 and 98 have been amended to recite ***stimulation*** of T cell responsiveness by the use of an ***anti-γ chain antibody***, thereby obviating the "modulation" issue raised by the Examiner under 35 U.S.C. §112, second paragraph. Support for these amendments can be found in the disclosure, for example, at page 6, line 6 through page 13, line 2.

In addition, claims 48 and 98 have been amended to incorporate the limitations of claims 54 and 101, respectively. As stated by the Examiner in the Office Action (Paper No. 15) at page 7, paragraph 14, claims 54 and 101 are free of the prior art. In view of the above amendments to claims 48 and 98, it is believed that these claims are free of the prior art. As all of the remaining claims are dependent from claim 48, it is believed that all of the pending claims are free of the prior art. Accordingly, in view of the above amendments and following remarks, Applicants submit that claims 48, 50, 55-61 and 97 and 98 are allowable.

In addition, the title of the specification has been amended to describe the claimed invention. Applicants respectfully submit that this amendment is sufficient to overcome the Examiner's objection to the title of the specification.

Applicants further submit that the above amendments raise no new issues which would require further consideration and/or search by the Examiner. Furthermore, in view of the amendments and arguments set forth herein, the number of issues for appeal have been reduced. For example, the Examiner's rejection under 35 U.S.C. 112, second paragraph, has been obviated by the amendments to claims 48 and 98.

Amendment and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

No new matter has been added. Applicants request that the amendments to the specification and claims be entered. For the Examiner's convenience, a copy of the claims as pending after the amendments herein, is presented in Appendix A.

Objection to the Title of the Specification

The Examiner asserts that the title of the present application, "Methods for Modulating T cell Responses by Manipulating a Common Cytokine Receptor Gamma Chain," is not descriptive and "should be restricted to the claimed invention."

Applicants respectfully submit that the amendment to the title is sufficient to overcome the Examiner's objection and respectfully request that this objection be reconsidered and withdrawn.

Acknowledgment of the Examiner's Withdrawal of Certain Rejections

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection of claims 98-101 under 35 U.S.C. §112, first and second paragraphs, as set forth in the Advisory Action (Paper No. 18) dated July 16, 1997.

Request for Reconsideration of the Finality of the Action

As previously set forth in the Amendment and Response after Final Pursuant to 37 C.F.R. §1.116 filed on June 27, 1997, Applicants requested reconsideration of the finality of Office Action (Paper No. 15). The final rejection was improperly issued in a second Office Action because it raised a new ground of rejection not necessitated by amendments. Applicants did not

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have an opportunity to respond to the new ground of rejection, nor develop clear issues before the advisability of an appeal.

In the Advisory Action (Paper No. 18) dated July 16, 1997 the Examiner failed to respond to Applicants request for reconsideration and failed to provide reasons in support of the finality of the Action. Applicants reasons in support of the request for reconsideration of the finality are reiterated below. In addition, Applicants have filed a Petition Under 37 C.F.R. §1.181 to Withdraw Finality of Rejection on even date herewith.

As previously set forth, Applicants respectfully submit that the Examiner has changed the grounds for the present rejection from those provided in the previous Office Action for reasons not necessitated by Applicants' amendments. Therefore, Applicants respectfully request that the finality of the present Office Action be withdrawn and that the present Amendment be treated as an Amendment submitted prior to a final Office Action (MPEP 706.07(a)).

In particular, the grounds for rejecting claims 48-61 and 97-101 relied on by the Examiner in the previous Office Action was that "*in vitro* and animal model studies have not correlated well with *in vivo* clinical trial results in patients and it is not clear that reliance on the *in vitro* experimental conditions accurately reflects the relative efficacy of the claimed therapeutic strategy to stimulate T cells (inhibit unresponsiveness)." The Examiner further stated that "there is no evidence that such an experimental model mimics the clinical situation." Thus, in the previous Office Action, the rejection was based on the Examiner's assertion that Applicants' disclosure fails to enable clinical application of the claimed methods.

However, in the present Office Action, the Examiner no longer relies on an asserted failure by Applicants to enable clinical application of the claimed methods. In fact, the Examiner "agrees" at page 4, lines 6-8, of the Action "that it is unnecessary that appellant must prove the ultimate value in humans of their asserted utility." Rather, the Examiner now states that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-

vivo." In particular, the Examiner states that "the issue involved is whether or not the evidence of record, based on in-vitro studies, is generally recognized by those of ordinary skill in the art, as being ***reasonably predictive of success in the practical in-vitro and in-vivo therapeutic methods encompassed by the instant claims***" (Emphasis added). The Examiner further states that the issue is "whether Applicants specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope of the broadly claimed therapeutic methods of modulating or inhibiting unresponsiveness in T cells."

In view of the above remarks, the final rejection was improperly issued in a second Office Action because it raised a new ground of rejection not necessitated by amendments. Applicants have been deprived of an opportunity to respond to the new ground of rejection or to develop clear issues before the advisability of an appeal. Accordingly, Applicants respectfully request that the finality of the present Office Action be reconsidered and withdrawn.

Rejection of Claims 48-61 and 97-101 Under 35 U.S.C. § 112, First Paragraph

Claims 48-61 and 97-101 are rejected under 35 U.S.C. §112, first paragraph, based on the Examiner's assertion that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo." In particular, the Examiner argues that "there is insufficient objective evidence to support the breadth and the predictability of modulating/inhibiting responsiveness of normal or primed T cells either ex-vivo as well as in-vivo." Moreover, the Examiner states that "the issue involved is whether or not the evidence of record, based on in-vitro studies, is generally recognized by those of ordinary skill in the art, as being ***reasonably predictive of success in the practical in-vitro and in-vivo therapeutic methods encompassed by the instant claims***." The Examiner further states that the issue is "whether Applicants specification provides insufficient information or nexus which enables any person skilled in the art to use the full scope

of the broadly claimed therapeutic methods of modulating or inhibiting unresponsiveness in T cells."

Applicants respectfully submit that this rejection does not apply to the claims as amended. Specifically, as amended, independent claims 48 and 98 are drawn to a method for stimulating T cell responsiveness by contacting a T cell which expresses a cytokine receptor γ chain with an anti-γ chain antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is stimulated. All of the remaining claims depend from claim 48. As the amended claims are directed to the use of an anti-γ chain antibody to stimulate T cell responsiveness, Applicants respectfully submit that the above-quoted rejection under 35 U.S.C. §112, first paragraph is obviated.

However, applicants wish to reiterate the following remarks in support of their position that the specification fully enables the claimed invention. The above quoted rejection of claims 48, 50, 55-61 and 97-98 is respectfully traversed on the grounds that the present specification does provide adequate guidance which would enable the ordinarily skilled artisan to make and use the claimed invention. First, it is respectfully submitted that the relevant question is whether the specification "adequately teaches one of ordinary skill in the art how to make or use ***the claimed invention***." The proper standard for judging enablement of claims involving an asserted therapeutic effect is whether the Applicants disclosure provides sufficient guidance and data which would lead one of ordinary skill in the art to ***reasonably*** believe the asserted utility or effect (*In re Brana* 51 F.3d 1560; 34 U.S.P.Q.2D 1437 (CAFC, decided March 30, 1995). The Court of Appeals for the Federal Circuit specifically held that if a patent disclosure presents a working description of an invention and data to support its utility which could be reasonably applied to *in vivo* systems, then further evidence should ***not*** be required to satisfy the enablement requirement of section 112, first paragraph, ***unless there is reason to doubt the objective truth*** of the asserted utility. As argued in the previous Amendment and Response to Final Rejection

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Pursuant to 37 C.F.R. §1.116, and further below, Applicants disclosure fully satisfies this enablement standard.

For example, Applicants specification teaches recombinant expression vectors for expressing proteins or peptides (i.e., an ***anti-γ chain antibody***) in cells (e.g., recombinant viral vectors), and nucleic acid delivery mechanisms suitable for gene therapy *in vitro* or *in vivo* at, for example, page 12, lines 26-35. Moreover, at page 18, line 16 through page 20, line 19, methods for administering agents, e.g., anti-γ chain antibodies, to subjects to stimulate T cell responses, are described. Further, Applicants disclosure provides specific, working examples demonstrating that agents within the scope of Applicants claim prevented the induction of T cell anergy in a human alloantigen specific T cell clonal model system (see Examples 1 and 2 on pages 21 and 23, respectively). The data presented in the specification is more than reasonably indicative of *in vivo* efficacy as asserted and claimed by Applicants. Human T cells and the cell lines described in the disclosure are routinely used to illustrate immune system responses *in vitro* and are art-accepted models of *in vivo* therapeutic efficacy.

In view of the above, the ordinarily skilled artisan would not have been required to use "undue experimentation" to practice the claimed invention as alleged by the Examiner. Thus, the ordinarily skilled artisan, following a careful reading of the above-described teachings from Applicants' specification can make and use the claimed invention. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 48, 56-61 and 98 Under U.S.C. §112 Second Paragraph

Claims 48, 56-61, 98 are rejected under U.S.C. §112 second paragraph as being indefinite and ambiguous in the recitation of the phrases "modulating T cell responsiveness" and "such that the T cell responsiveness is modulated" in the absence of a clear positive or negative effect. In particular, the Examiner states that the term "modulation" is not appropriate "because modulation

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can occur both in positive and negative directions and applicant elected methods of stimulating T cells."

Applicants respectfully submit that the above rejection does not apply to the claims as amended. In particular, claims 48 and 98 have been amended as suggested by the Examiner to recite "[a] method for ***stimulating*** T cell responsiveness." Accordingly, in view of the cancellation and amendments to these claims the Examiner's rejection under 35 U.S.C. 112, second paragraph, has been obviated.

Rejection of claims 48-53, 55-58, 60-61, 97-100 Under U.S.C. § 102

Claims 48-53, 55-58, 60-61, 97-100 stand rejected under U.S.C. § 102(e) as being anticipated by Plunkett et al. (U.S. Patent No. 5,382,427). Claims 48-53, 55-61 and 97-100 stand rejected under U.S.C. § 102(b) as being anticipated by Lee et al. (U.S. Patent No. 5,017,691). Claims 48-53, 55-61 and 97-100 stand rejected under U.S.C. § 102(a)(e) as being anticipated by Lynch et al. (U. S. Patent No. 5,229,115). Claims 48-53, 59, 61, 97-100 stand rejected under U.S.C. § 102(e) as being anticipated by Grabstein et al. (U.S. Patent No.5, 474,769). The Examiner asserts that the cytokines and methods of use taught in each of the aforementioned references meet the limitations of the presently claimed methods, and that the functional limitations recited in the present claims "would be addressed by the inherent properties of the referenced methods."

Applicants respectfully submit that the above rejection does not apply to the claims as amended. Specifically, claims 48 and 98 have been amended to incorporate the limitations of claims 54 and 101 which were indicated by the Examiner in Paper No. 15, page 7, paragraph 14, to be free of the prior art. Accordingly, Applicants submit that claims 48 and 98, as well as claims 50, 55-61, 97 and 98 which depend from claim 48, are free of the prior art. Therefore, Applicants respectfully request that the section 102 rejections be reconsidered and withdrawn.

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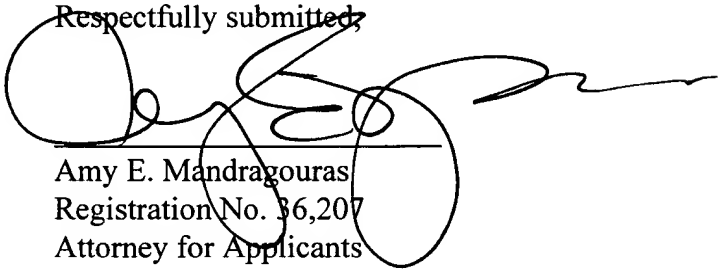
CONCLUSION

Reconsideration and allowance of claims 48, 50, 55-61 and 97-98 is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Dated: December 16, 1997

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APPENDIX A

48. A method for stimulating T cell responsiveness, comprising contacting a T cell which expresses a cytokine receptor γ chain with an anti-γ chain antibody which binds to and transduces a signal via the γ chain such that T cell responsiveness is stimulated.

50. The method of claim 48, wherein the T cell has received a primary activation signal in the absence of a costimulatory signal.

55. The method of claim 48, wherein the T cell is contacted *in vivo* with the anti-γ chain antibody.

56. The method of claim 48, further comprising contacting the T cell with an agent which stimulates a primary activation signal in the T cell.

57. The method of claim 56, further comprising contacting the T cell with an agent which stimulates a costimulatory signal in the T cell.

58. The method of claim 56, wherein the agent which stimulates a primary activation signal in the T cell is an antigen.

59. The method of claim 58, wherein the antigen is a pathogen or portion thereof selected from the group consisting of a virus, a bacteria, and a parasite

60. The method of claim 58, wherein the antigen is a tumor antigen.

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61. The method of claim 58, wherein the T cell is contacted with the antigen *in vivo*.

97. The method of claim 50, wherein the T cell is contacted with the agent *in vitro*.

98. A method for stimulating responsiveness in an anergic T cell, comprising contacting said T cell with an anti-γ chain antibody which transduces a signal via the cytokine receptor γ chain such that T cell responsiveness is stimulated.

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